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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,066	ALPAR ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-56,58-63,66 and 68-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-56,58-63,66 and 68-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/31/09 & 7/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1 The amendment filed August 31, 2009 has been entered. Claims 52-56, 58, 61-63, 66, 68, and 71 have been amended. Claims 1-51, 57, 64-65 and 67 are cancelled. Claims 52-56, 58-63, 66 and 68-71 are under consideration in this office action.

Withdrawal of Rejections

3. The following objections and rejections have been withdrawn in view of applicants' amendments and arguments:

a) The objections of claims 44-71;

b) The rejection of claims 1, 5-6, 11-15, 20, 44-48, 51, 62, 65-68 and 71 under 35 U.S.C. 102(a) as being anticipated by Amsden et al., (WO 99/57176);

c) The rejection of claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62, and 65-71 under 35 U.S.C. 103(a) as being unpatentable over Eyles in view of Amsden et al;

d) The rejection of claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62, and 65-71 under 35 U.S.C. 103(a) as being unpatentable over Illum in view of in view of Amsden et al;

e) The rejection of claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62, and 65-71 under 35 U.S.C. 103(a) as being unpatentable over Duncan et al., in view of in view of Amsden et al; and

f) The rejection of claims 1, 5-6, 11-17, 20-22, 37, 44-51, 62, and 65-71 under 35 U.S.C. 103(a) as being unpatentable over Illum or Eyles and Amsden in view of in view of Duncan et al.

Response to Arguments

4. Applicant's arguments filed August 31, 2009 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 52, 55-56, 58-63, 66 and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) and Amsden et al., (WO 99/57176) further in view of Duncan et al., (WO 94/20070 published September 1994).

The claims are drawn to a pharmaceutical composition comprising particles comprising a polymeric material, a biologically active agent capable of generating a protective immune response in an animal or human, a cationic Pluronic™ and N-carboxymethyl chitosan or a salt thereof.

The claims are drawn to a pharmaceutical composition comprising an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof and particles comprising a polymeric material, a cationic Pluronic™ and a biologically active agent capable of generating a protective immune response in an animal or human.

The claims are also drawn to a pharmaceutical composition comprising particles comprising a polymeric material, a cationic Pluronic™ and a biologically active agent capable of generating a protective immune response in an animal or human, wherein the particles are coated with the a N-carboxymethyl chitosan or a salt thereof and the biologically active agent is adsorbed onto the coated particles.

Eyles et al., teach a pharmaceutical composition comprising poly-(L-lactide) microspheres co-encapsulated with *Yersinia pestis* V and F1 subunits that confer protection from pneumonic plague in mice (page 699, col.2). Eyles et al., teach that the F1 antigen confers resistance to phagocytosis and both F1 and V antigens are protective, although there is an additive effect in the combination (page 698, col.2). It is noted that the F1 peptide subunit is a glycoprotein. The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and was used in a modified double emulsion solvent evaporation method (page 699, col.2). Eyles et al., teach effective vaccination requires affecting or utilizing musocal surfaces as portals of entry (page 698-699, col.2-1). Furthermore Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). Eyles teach that simple mucosal applications are ineffective because of enzymatic or chemical destruction, combined with poor absorption; therefore encapsulation of antigenic material within microparticulate polymeric carriers such as poly-DL-lactide protect the vaccines from degradation and enhance mucosal and systemic absorption (page 699,

col.1). However Eyles et al., do not teach pharmaceutical compositions comprising N-carboxymethyl chitosan or cationic Pluronic™.

Amsden et al., teach the application of microspheres composed of biodegradable, biocompatible polymer and contains a bioactive agent dispersed therein (page 23, lines 3-6). Amsden et al., teach delivering a bioactive agent to a subject in need of treatment (page 23, lines 15-16). Examples of suitable bioactive agents include anti-proliferative agents, steroids, analgesics, narcotic antagonists, antibiotics, anti-fungals, anti-histamines, anti-asthmatics, B-blockers and anti-cancer agents (page 23, lines 18-23). Amsden et al., teach therapeutic microspheres comprising a bioactive agent being a pharmacologically active peptide, antigen, or antibody explemplified by a microsphere that bears an infectious agent antigen for vaccination (page 24, lines 1-3). Microsphere which comprise bioactive agents are incorporated within the microsphere and /or be bound to the surface (page 24, lines 3-5). Amsden et al., teach the composition formed into microspheres composed of hydrophilic polymers selected from polysaccharides such as chitosan, N,O-carbomethyl chitosan, O-carboxymethyl chitosan, N-carboxymethyl chitosan, blends, copolymers and combinations of these polymers (page 9, lines 12-26). Amsden et al., teach the first composition being poly(lactide) and a second composition being co-glycolide or poly(glycolide) at a ratio of 85:15 , see Example 1 at page 26. Amsden et al., teach microspheres incorporated into a second polymer, which are uniformly sized microspheres dispersed throughout a gel or viscous solution or dispersed throughout a solid biodegradable polymer scaffold (page 24, lines 7-10). Amsden et al., teach that polycationic carbohydrates capable of

forming particles from 99:1 to 9:1 w/w include chitin derivatives, chitosans, cationic polypeptides, polyamino acids; which are all disclosed by Amsden et al. Amsden et al., teach polymers formed into microspheres composed of poly(lactide-co-glycolide) (PGLA) and other lipophilic polymers such as polyesters including but not limited to poly-(L-lactide), poly(lactide) as well as protein or polypeptide such as poly(amino acids). It is noted that is a polymeric material has a molecular weight of 100 kDa or more. However Amsden et al., do not teach the inclusion of a cationic Pluronic™.

Duncan et al., teach compositions comprising: i) biologically active agents, such as immunogens or antigens at pages 4-5 para.1, ii) an adjuvant chemical having adjuvant properties wherein the adjuvants include Pluronic™ block copolymers also known as cationic Pluronics™ and polyamino acids such as polyarnithine at pages 9-10, para. 1; and iii) an acceptable carrier such as a mucoadhesive at page 6, para.1. Duncan et al., further teach that an enhancement in the immune response is observed when the adjuvant is combined with the immunogen and mucoadhesive (pages 10-11, para.2). The antigens are more immunogenic when they are incorporated into the polymeric microparticles, nanoparticles or liposomes (page 2, para.4).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known N-carboxymethyl chitosan as taught by Amsden et al., and modify the compositions to include the biologically active antigen and agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Eyles and further incorporate the cationic Pluronic™ having adjuvant like properties of Duncan et al., in order to enhance the

muchoadhesive properties for the compositon of Eyles and Amsden. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Eyles and Amsden because Duncan et al., teach the need for mucoadhesive which provide further enhancement in the immune response. Thus one of ordinary skill in the art would have a reasonable expectation of success and no more than routine skill would have been required to modify the composition of Eyles to incorporate the N-carboxymethyl-chitosan of Amsden et al., into the pharmaceutical composition which already comprises a mucoadhesive combined with biological active antigens and cationic Pluronic™ in microparticle formation to achieve enhanced mucosal absorption.

Response to Arguments

6. Applicant's arguments have been fully considered but they are not persuasive. The response to arguments regarding Amsden and Duncan are discussed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 52, 55-56, 58, 61-63, 66, 68 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amsden et al., (WO 99/57176) in view of Duncan et al., (WO 94/20070 published September 1994).

Amsden et al., has been discussed above as teaching compositions comprising particles comprising a polymeric material, a biologically active agent capable of generating a protective immune response in an animal or human, and N-carboxymethyl chitosan or a salt thereof. However, Amsden et al., do not teach the composition further comprising a cationic Pluronic™.

As previously disclosed, Duncan et al., teach compositions comprising biologically active agents, such as immunogens or antigens being more immunogenic when they are incorporated into the polymeric microparticles, nanoparticles; Pluronic™ block copolymers; and mucoadhesive for enhancement in the immune.

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known N-carboxymethyl chitosan as taught by Amsden et al., and modify the compositions to include the biologically active antigen and agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Duncan et al., in order to enhance the muchoadhesive properties. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Duncan et al., because Duncan et al., teach the need for mucoadhesive which provide further enhancement in the immune response. Thus one of ordinary skill in the art would have a reasonable expectation of success in providing compositions having N-

carboxymethyl-chitosan since Amsden et al., teach it is well known to provide pharmaceutical compositions comprising N-carboxymethyl-chitosan are effective in patients. No more than routine would have been required to modify the composition of Duncan et al., to instead incorporate the N-carboxymethyl-chitosan into the pharmaceutical composition of Duncan which already comprises a mucoadhesive combined with biological active antigens and cationic Pluronic™ in microparticle formation to achieve enhanced mucosal absorption. Finally it would have been advantageous to incorporate N-carboxymethyl-chitosan in the pharmaceutical composition, in order to achieve an enhanced effect upon the host.

Response to Arguments

8. Applicant's arguments filed August 31, 2009 have been fully considered but they are not persuasive. The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Amsden et al., in view of Duncan et al., is maintained.

Applicants' agree that Duncan et al., disclose the use of Pluronic™ block copolymers within their pharmaceutical compositions; however applicants assert that Duncan fails to suggest that copolymers are used in order to improve their immunogencity. Duncan et al., provides a pharmaceutical composition comprising an infectious agent, a mucoadhesive and an adjuvant to boost the immune response to the antigen in an animal (abstract). Duncan teaches that adjuvants enhance the magnitude or duration of the immune response (page 8, para. 3). Duncan et al., teach surface active agents having adjuvant activity are employed, including Pluronic™ block

copolymers. Additionally, Amsden et al., teach the inclusion of microsphere stabilizing agents (page 6, lines 3-6). Therefore contrary to applicants' argument, Duncan et al., do teach that the cationic copolymer does improve immunogenicity and create stable emulsions.

Applicants argue that Duncan uses the cationic copolymers to make squalene emulsions stable, which is a different use than applicants. However there is no requirement that Duncan need to suggest or provide reasoning for improving the pharmaceutical composition. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). In *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (Fed. Cir. 2004), the court stated that "just as the discovery of properties of a known material does not make it novel, the identification and characterization of a prior art material also does not make it novel." There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent and disclosed in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Therefore, Duncan et al., do not need to provide the same reason for including cationic copolymers within the

pharmaceutical composition, because Duncan et al., clearly teach the inclusion of cationic copolymers within the pharmaceutical composition. Therefore the rejection is maintained.

New Grounds of Rejection Necessitated By Amendment

Claim Rejections - 35 USC § 103

9. Claims 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amsden et al., (WO 99/57176) and Duncan et al., as applied to claim 52, further in view of Cleary et al., (WO 96/21432 published July 18, 1996).

Both Amsden et al., and Duncan et al., have been discussed above as teaching a pharmaceutical composition comprising particles comprising a polymeric material, a biologically active agent capable of generating a protective immune response in an animal or human, a cationic Pluronic™ and N-carboxymethyl chitosan. However none specifically recite the particles being surface-modified, coated with or absorbed with N-carboxymethyl chitosan.

Clearly et al., teach sustained and controlled local and systemic release of active agents to adhere to mucosal surfaces (page 3, lines 9-12). Cleary et al., teach the active agents have therapeutic effects either locally, upon the mucosal tissues and underlying tissues or systemically delivered (page 3-4, lines 26-2). Cleary et al., teach mucoadhesive particles having a polymer which is the mucoadhesive itself in particulate form (page 4-5, lines 26-1). Clearly et al., teach the particles as being microspheres, microparticles or microcapsules (page 5, lines 5-6). Cleary et al., teach coating the

active substance with a bioerodible mucoadhesive polymer layer (page 7, line 1). Cleary et al., teach a particle having a drug containing core and a mucoadhesive coating made of a polymer that dissolves slowing resulting in retention of the active substance on the mucosal surface for an extended period of time (page 7, lines 5-15).

Therefore it would have been prima facie obvious at the time of applicants' invention to modify the pharmaceutical composition comprising a polymeric material, a biologically active agent, a cationic Pluronic™ and N-carboxymethyl chitosan as taught by Amsden et al., and Duncan et al., wherein the modification incorporates the having the mucoadhesive at the surface of the particle as taught by Cleary et al., in order to provide sustained and controlled local and systemic release of active agents to mucosal surfaces. One of ordinary skill in the art would be motivated to modify the compositions as taught by Amsden et al., and Duncan et al., because Duncan et al.., teach the inclusion of a mucoadhesive is well known and that mucosal absorption enhancers the immune response of antigens. All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combinations would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 52-56, 58-63, 66 and 68-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim scope is uncertain since the trademark Pluronics ™ or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a particular material, i.e. cationic block copolymers and accordingly, the identification is indefinite. Furthermore, the use of trademarks is improper since products identified by trademarks are within the sole control of the trademark owner and are subject to change by said owner at their discretion.

Conclusion

11. No claims allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645